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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Rhythm Control in Heart Failure Patients With Atrial Fibrillation

Contemporary Challenges Including the Role of Ablation

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ABSTRACT

Because nonpharmacological interventions likely alter the risks and benefits associated with rhythm control, this paper reviews the role of current rhythm control strategies in atrial fibrillation. This report also focuses on the specific limitations of pharmacological interventions and the utility of percutaneous ablation in this growing population of patients with concomitant atrial fibrillation and heart failure. (J Am Coll Cardiol 2014;64:710–21) © 2014 by the American College of Cardiology Foundation.

Atrial fibrillation (AF) and heart failure (HF) loom as 2 burgeoning public health problems that impair quality of life (QOL) and reduce longevity (1,2). Both can beget and/or accentuate the severity of the other, and synergistically confer worse outcomes when compared with patients with either condition alone (3). Despite extensive comparisons between rate and rhythm control for AF, neither strategy has proven to be superior in patients with (4) or without (5) HF. However, these trials strictly tested medical therapy and were limited by substantial crossover, suboptimal therapeutic efficacy, and adverse effects of pharmacological therapy (4–6).

EPIDEMIOLOGY

AF is the most common cardiac arrhythmia and affects more than 33 million individuals across the globe. Due in part to the aging population, each year more than 5 million people develop AF worldwide (7). The increase in obesity and sleep apnea has also been implicated in the increasing prevalence of AF (8,9). In persons ages 55 years and older, the lifetime risk of AF is approximately 25% in men and 22% to 23% in women (10,11). Importantly, this arrhythmia carries risk for significant morbidity, including thromboembolic stroke, tachycardia-induced cardiomyopathy, and debilitating symptoms. AF not only impairs QOL (2), it also is associated with diminished survival. The Framingham Heart Study reported 10-year death rates in individuals with AF at 61% and 58% in men and women, respectively, compared with 30% and 21% in men and women without AF (1).

HF, a diagnosis that encompasses those with both preserved and reduced ejection fractions (EF), is also increasingly prevalent (12). As the care for coronary artery disease and acute coronary syndromes improves, the incidence of ischemic cardiomyopathy has increased accordingly. Population studies suggest that the prevalence of HF has doubled over the past

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decade (12,13). Irrespective of etiology, a diagnosis of HF carries a poor prognosis, with an estimated 5-year survival of 25% to 38% (13).

SYMPTOM BURDEN, QUALITY OF LIFE, AND STROKE RISK

QOL is impaired in patients with AF and HF, both alone and in concert (2), with the primary drivers of this deterioration of QOL being one's perception of health, physical symptoms, and financial burden. A QOL analysis of the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial demonstrated improved QOL in those treated with either rate or rhythm control therapies (14). The failure of rhythm control to yield superior QOL compared with rate control may have been due to the limited effectiveness or adverse effects of antiarrhythmic therapy despite the advantages of sinus rhythm.

Similar results were reported in the AF-CHF (Atrial Fibrillation and Congestive Heart Failure) trial (15), where both rate and rhythm control improved symptoms, but sinus rhythm had the added benefit of being associated with improved New York Heart Association functional class and QOL. Importantly, impaired QOL in patients with AF and HF appears to predict both hospitalization and mortality (16), thus highlighting the importance of treatment and, potentially, the restoration of sinus rhythm.

AF increases stroke risk several fold (17), and AF-related strokes are associated with significantly reduced QOL, disability, and mortality (18). Not surprisingly, an analysis of the AFFIRM study failed to show a significant difference in stroke risk between the rate and rhythm control arms, although a post-hoc analysis suggested that the presence of AF was associated with an increased risk of ischemic stroke, whereas sinus rhythm and systemic anticoagulation were associated with a lower risk of stroke (19).

Subsequent studies have continued to raise the hypothesis that the reduction and/or elimination of AF decreases stroke risk. Recently, a retrospective observational analysis of age- and sex-matched patients suggested that catheter ablation of AF was associated with a lower risk of incident stroke (20). Across all $CHADS_2$ profiles, patients who underwent ablation demonstrated lower long-term risk of stroke than those with AF who did not undergo ablation. It should be noted that this study did not fully adjust for clinically important covariates that could influence stroke risk. Additionally, the average EF in the ablation group was 58%, and data regarding maintenance of sinus rhythm in follow-up were not available. Nevertheless, these data raise the possibility that successful ablation of AF may significantly modify long-term stroke risk in patients with AF. Other studies also have reported very low rates of thromboembolic events after successful AF ablation (21,22), albeit in populations with relatively low CHA_2DS_2-VASc scores. Whether or not AF ablation can reduce the risk of stroke in patients with and without HF will require large randomized studies such as the CABANA (Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation), RAFT AF (A Randomized Ablation-based Atrial Fibrillation Rhythm Control Versus Rate Control Trial in Patients With Heart Failure and High Burden Atrial Fibrillation), and the CASTLE-AF (Catheter Ablation Versus Standard Conventional Treatment in Patients With Left Ventricular Dysfunction and Atrial Fibrillation) trials.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
EF = ejection fraction
FIRM = focal impulse and rotor modulation
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
LV = left ventricular
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
PVI = pulmonary vein isolation
QOL = quality of life
RAAS = renin-angiotensin-aldosterone system

SHARED MECHANISMS IN AF AND HF

As heterogeneous syndromes, AF and HF often represent the culmination of many adverse physiological conditions, including common cardiovascular disorders such as hypertension and coronary ischemia. Indeed, AF and HF may be considered "chamber-specific expressions" of global myocardial damage. That is, analogous cellular abnormalities in the atria and ventricles, resulting from diverse underlying pathologies and genetic predisposition, may manifest as electrical abnormalities and fibrillation in the atria and pump failure with elevated risk of fibrillation in the ventricles—although the reciprocals are also observed (23). Increasingly appreciated morbid conditions/risk factors including obesity, tobacco use, hypertension, diabetes, kidney disease, sleep apnea, and coronary disease are primary drivers of this process. Not unexpectedly, multiple large cohorts have described these comorbidities and environmental influences as independent risk factors for both AF and HF. **Figure 1** illustrates this shared relationship between diverse conditions and the pathogenesis of AF and HF.

In addition to their shared underlying risk factors, AF and HF also are independent risk factors for one another (3,24). Among persons with HF, the prevalence of AF ranges between 15% and 50% (**Fig. 2**). Although it remains uncertain whether AF independently portends increased mortality in patients with HF, it is an independent predictor of worsening left ventricular (LV) function and impaired QOL

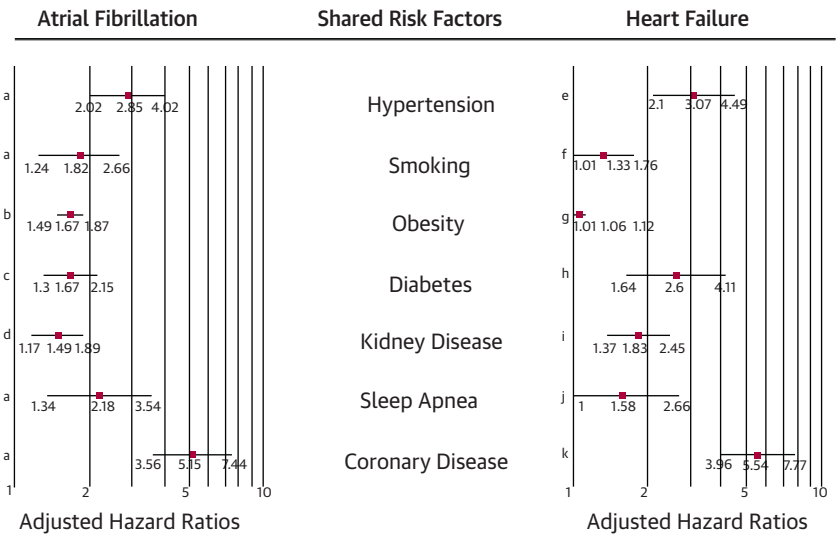


FIGURE 1 Hazard Ratio of Incident AF and HF According to Shared Risk Factors

Adjusted hazard ratios (95% confidence limits) of atrial fibrillation (AF) **(left)** and heart failure (HF) **(right)** according to 7 shared risk factors. These data were gathered through studies of various cohorts. If overall cohort data were unavailable or not reported, results from white and/or male patients (both the largest subgroups) were reported. References: a = (91); b = (92); c = (93); d = (94); e = (95); f = (96); g = (97); h = (98); i = (99); j = (100); k = (101).

(1,24–26). In a retrospective analysis of the SOLVD (Studies Of Left Ventricular Dysfunction) trial, Dries et al. (25) found that AF was significantly associated with increased mortality in patients with AF versus sinus rhythm who had underlying asymptomatic or symptomatic LV dysfunction. Numerous studies corroborate the association of poorer overall prognosis in patients with AF or HF and the development of the other (3,25,27,28).

ATRIAL FUNCTION AND CARDIAC PERFORMANCE

As depicted in the **Central Illustration**, much effort has been spent in understanding the causal processes and shared mechanisms between AF and HF. Though multifactorial, key organ-level and subcellular pathophysiologic processes have been elucidated. There exist numerous mechanisms through which a diseased ventricle may promote atrial tachyarrhythmias. Hemodynamically, elevated ventricular filling pressures, functional valvular regurgitation, and renin-angiotensin-aldosterone system (RAAS)-induced volume retention promote left atrial dilation. Mechanically, stretching of the myocardium enhances pulmonary venous ectopy (the most common AF trigger) (29), promotes re-entry, and slows conduction; all of these actions promote the onset of AF (30–33). Neurohormonally, RAAS activation and increased circulating levels of angiotensin II lead to atrial fibrosis and anisotropy (34). Myocardial fibrosis heralds electrical dysfunction, including slowed and heterogenous conduction times that facilitate wave break. These changes expedite the development and persistence of additional AF triggers and AF perpetuators, including electrical spiral waves (rotors) and focal sources (35). Finally, cellular calcium dysregulation occurs in HF as a result of altered myocardial contraction function and modified calcium channel concentration, but has important electrophysiological consequences as well. Calcium overload likely facilitates abnormal action potential durations within the atria that have been associated with both increased AF triggers as well as enablement of re-entry (36).

Atrial contraction plays an important role in ventricular filling. Loss of atrial systole can lead to as much as a 25% reduction in cardiac output, although this reduction is exaggerated when ventricular compliance is limited (37). Additionally, irregularity of ventricular cycle lengths (regardless of atrial function or ventricular rate) reduces cardiac output (38). Uncontrolled, irregular, and rapid ventricular conduction in the setting of inefficient and impaired

cardiac output can lead to ventricular dysfunction and tachycardia-mediated cardiomyopathy (37,39). However, immediately after cardioversion, increases in stroke volume and left ventricular ejection fraction (LVEF) are observed, despite the absence of demonstrable improvement in contractility (40). These physiological observations serve as the primary rationale behind strategies to prevent recurrent arrhythmia and maintain sinus rhythm in AF patients with and without underlying cardiovascular disease.

PHARMACOLOGICAL RHYTHM CONTROL CONSIDERATIONS

Multiple studies have compared pharmacological rate and rhythm strategies but have failed to identify a superior therapy, a finding that extends to patients with HF (4,41). Nevertheless, these trials actually tested medical therapeutic strategies and did not truly compare rate versus rhythm control because of substantial crossovers between treatment arms; specifically, patients receiving antiarrhythmic therapy were often in AF, whereas patients receiving rate control therapy were often in sinus rhythm. Finally, these studies were limited, not only by suboptimal efficacy, but also by the adverse effects of pharmacological therapy.

Antiarrhythmic drug therapy is indicated as first-line therapy for AF that remains symptomatic despite adequate rate control (42). Unfortunately, many antiarrhythmic drugs are contraindicated in patients with structural heart disease, and those that are not have significant side effects and/or toxicities (42). Amiodarone and dofetilide are the lone guideline-recommended antiarrhythmic medications for patients with symptomatic HF or significant LV dysfunction, yet they have significant adverse effects and drug-drug interactions (43). Amiodarone, for example, carries the risk of pulmonary, hepatic, and thyroid toxicity (44). Despite its potency, recurrence rates in patients with AF and HF are 50% or greater at 1 year (45). Equally concerning, a chief risk of dofetilide therapy is that it prolongs the QT interval and can lead to torsades in 0.8% to 3.3% of those treated. To mitigate these risks, initiation of dofetilide requires a 3-day hospitalization for careful monitoring. Moreover, dofetilide is renally cleared and must be adjusted (if used at all) in patients with renal dysfunction, which commonly accompanies HF (44).

Pre-clinical development of AF therapies has increased significantly, and there are several novel therapeutic modalities on the horizon. Furthermore, the development of biomarkers for AF disease severity and response to treatment may also transform our approach to AF care. These advances have highlighted the need for a future personalized approach to AF management (46). Well-known for its antianginal properties and limited side-effect profile, ranolazine is being studied increasingly in HF and AF. A late sodium-channel antagonist, ranolazine promotes myocardial relaxation by decreasing intracellular calcium and has been shown to reduce atrial and ventricular arrhythmias (47,48). It has been reported as an effective synergistic adjunct to amiodarone for AF (49,50) and is currently being studied as a lone antiarrhythmic drug and in fixed-dose combination with dronedarone (51). Budiodarone, an amiodarone analogue with a shorter half-life and alternative metabolism, has been investigated for AF rhythm control with the hope of producing fewer side effects (52); to date, studies aimed primarily at an HF population do not exist. Genotype-directed therapy for AF is another promising line of investigation and another possible means of personalizing AF treatment. Beta-blocker therapy tailored to beta-adrenergic receptor genotype is 1 such possibility. Patients with HF who are β_1 adrenergic receptor 389 Arg homozygotes exhibit a significant reduction in new-onset AF when treated with bucindolol (vs. placebo) when compared with $\beta_1$389 Gly carriers (hazard ratio: 0.26, 95% confidence interval: 0.12 to 0.57 vs. hazard ratio: 1.01, 95% confidence interval:

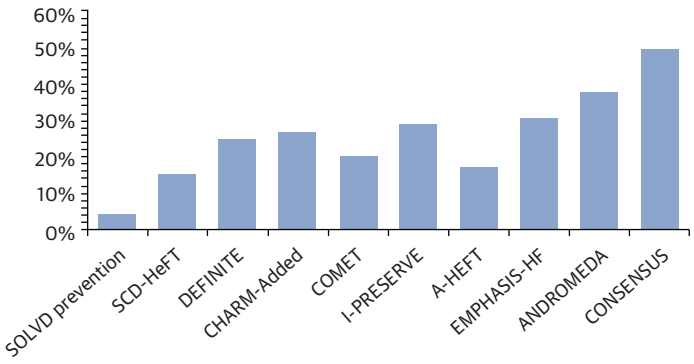
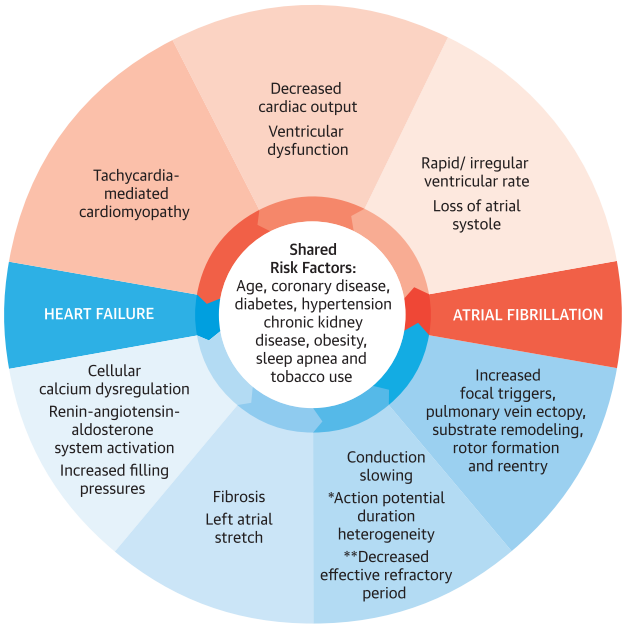


FIGURE 2 Prevalence of AF in Patients Enrolled in HF Studies

The bars represent percentages of patients with HF who had concomitant AF at enrollment in 10 clinical trials. Studies include SOLVD (Studies of Left Ventricular Dysfunction) (25); SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) (102); DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation) (103); CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality) (104); I-PRESERVE (Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction) (105); A-HeFT (African-American Heart Failure Trial) (106); EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) (107); ANDROMEDA (Increased Mortality After Dronedarone Therapy for Severe Heart Failure) (108); and CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) (109). Other abbreviations as in **Figure 1**.



CENTRAL ILLUSTRATION The Physiological Relationship Between Atrial Fibrillation and Heart Failure

*Action potential duration heterogeneity includes spatial and temporal nonuniformities (36). **This mechanistic hypothesis has fallen out of favor with recent evidence (33).

0.56 to 1.84; p for interaction = 0.008) (53). The ongoing GENETIC-AF (Genetically Targeted Therapy for the Prevention of Symptomatic Atrial Fibrillation in Patients With Heart Failure) clinical trial will test the hypothesis that genotype-directed bucindolol therapy is superior to metoprolol for the prevention of symptomatic AF in patients with HF.

CATHETER ABLATION FOR RHYTHM AND SYMPTOM CONTROL

ABLATION TECHNIQUE. Given the limitations of current antiarrhythmic drug therapy, clinicians have shown great interest in the use of nonpharmacological rhythm control interventions in patients with AF and HF. The role of catheter ablation is not simply to restore and maintain sinus rhythm, but more importantly, to ameliorate symptoms and improve QOL. The percutaneous technique, at a minimum, employs circumferential ablation and hence electrical isolation of the pulmonary veins and their connection to atrial myocardium. Additional ablation, such as linear ablation and/or focal ablations of areas with evidence of scar, fractionation, or rotor-perpetuation, may be employed, too, depending upon the type of AF and degree of left atrial disease (**Fig. 3**) (54–56). Ablation of complex fractionated atrial electrograms as an adjunct to pulmonary vein isolation (PVI) has been demonstrated to increase freedom from AF compared with PVI alone (55,57). Several investigators have demonstrated that the focal impulse and rotor modulation (FIRM) technique, distinct from PVI, can successfully identify ablative targets, called rotors, and terminate or slow AF and improve arrhythmia-free outcomes compared with conventional ablation alone (56,57). As our understanding of the mechanisms behind AF initiation and propagation continues to advance, durable targets for novel therapies are evolving in tandem (58).

ABLATION VERSUS ANTIARRHYTHMIC DRUG THERAPY. Although the efficacy of catheter ablation varies according to the underlying severity and duration of AF, multiple studies have established its superiority in those patients with recurrent AF despite antiarrhythmic drug therapy (59,60). Meta-analyses of clinical trials have concluded PVI to be superior to antiarrhythmic drug therapy as a second-line therapy for maintaining sinus rhythm, improving physical functioning, and potentially, reducing readmission rates for patients with symptomatic AF (60,61). Initial studies comparing antiarrhythmic drug therapy versus catheter ablation as initial therapy in treatment-naive patients with paroxysmal AF have revealed conflicting results (62,63); hence, catheter ablation is not typically employed as first-line therapy. However, a recent clinical trial demonstrated a significant attributable benefit of catheter ablation compared with antiarrhythmic therapy as first-line therapy for preventing recurrent atrial tachyarrhythmias at 2 years (64). Notably, these studies were not primarily performed in patients with HF, and many of the antiarrhythmic medications used are contraindicated in patients with HF. To date, there are no studies investigating catheter ablation as first-line treatment for AF in HF patients. Although some trials include freedom from antiarrhythmic drugs as a therapeutic endpoint of catheter ablation, it should be noted that the 2 interventions may be synergistic or even necessary to ameliorate AF-associated symptoms and potentially restore sinus rhythm.

EFFICACY AND OUTCOMES FOR CATHETER ABLATION. Importantly, studies citing the highest success rates of catheter ablation are composed primarily of middle-aged men with few comorbidities and often included repeat or redo ablation procedures. A smaller number of trials have been performed in dedicated cohorts with AF and concomitant HF. **Table 1** details and reviews the available

observational and randomized studies of catheter ablation in this patient population.

Initial studies sought to identify success/failure rates of catheter ablation in patients with and without HF. At 15-month follow-up, Chen et al. (65) reported 13% of patients with normal EF developed recurrent AF versus 27% in those with reduced EF ($p = 0.03$), despite similar risk profiles. However, after including outcomes following a second procedure, 96% of patients with reduced EF remained in sinus rhythm during follow-up without antiarrhythmic drug therapy. Importantly, both groups experienced significant improvement in QOL. Gentlesk et al. (66) reported a somewhat similar experience in a 2007 study, which found no difference in success rates of catheter ablation in patients with and without LV dysfunction (86% vs. 87%), though patients with reduced EF more often required repeat ablation. In patients with LV dysfunction, maintenance of sinus rhythm resulted in an average absolute increase in EF of 14%. These studies highlight the need for randomized trials to better evaluate the role and efficacy of ablative therapy.

An alternative procedure, atrioventricular node ablation with pacing, has shown efficacy in patients with refractory AF and HF (67). To compare the extremes of rate and rhythm control strategies, the PABA-CHF (Pulmonary Vein Antrum Isolation versus AV Node Ablation with Bi-Ventricular Pacing for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure) study randomized 41 patients to atrioventricular node ablation and subsequent biventricular pacing versus PVI (68). At 6-month follow-up, the PVI group had 88% AF-free survival and an absolute increase in LVEF of 8% versus no change in the biventricular pacing/nodal ablation group ($p < 0.001$). Functional capacity was enhanced with PVI based on significant improvements in both the 6-min walk test and QOL. The outcomes suggest that atrioventricular node ablation and pacing was inferior to PVI, but the study did not evaluate the less invasive, more common strategy of pharmacological rate control.

Several clinical trials have since compared pharmacological rate control with AF ablation (PVI ± focal substrate ablation). The first of these trials demonstrated a nonsignificant trend toward LVEF improvement in the ablation group, without significant between-group differences in QOL or exercise capacity (69). Limitations of the study included only 50% maintenance of sinus rhythm in the ablation group and a higher-than-expected maintenance of sinus rhythm in the rate control arm. Two trials have since reported significant improvement in QOL and exercise capacity after ablation compared with usual rate control therapies (70,71). Specifically, the ARC-HF (A Randomised Trial to Assess Catheter Ablation Versus Rate Control in the Management of Persistent Atrial Fibrillation in Chronic Heart Failure) investigators (71) reported a trend toward EF improvement in the ablation group at 12 months, whereas the CAMTAF (Catheter Ablation Versus Medical Treatment of AF in Heart Failure) trial (70) found significant improvement at 6 months. The aforementioned studies primarily enrolled and aimed to evaluate patients with HF and reduced EF; the CAMTAF trial was notable in that the inclusion EF cutoff was ≤50% compared with the more typical 35% cutoff in the other trials. However, the average LVEF in the CAMTAF trial was still significantly reduced at 32% pre-intervention. This is notable because there remains a paucity of data surrounding AF therapies in the setting of heart failure with preserved ejection fraction (HFpEF). It stands to reason, as in HF with reduced EF, that patients with HFpEF would also benefit from atrioventricular synchrony. Emerging data from a single-center study indicates that catheter ablation success rates in patients with HFpEF are similar to those without ventricular dysfunction and resultant sinus rhythm is associated with improved systolic and diastolic

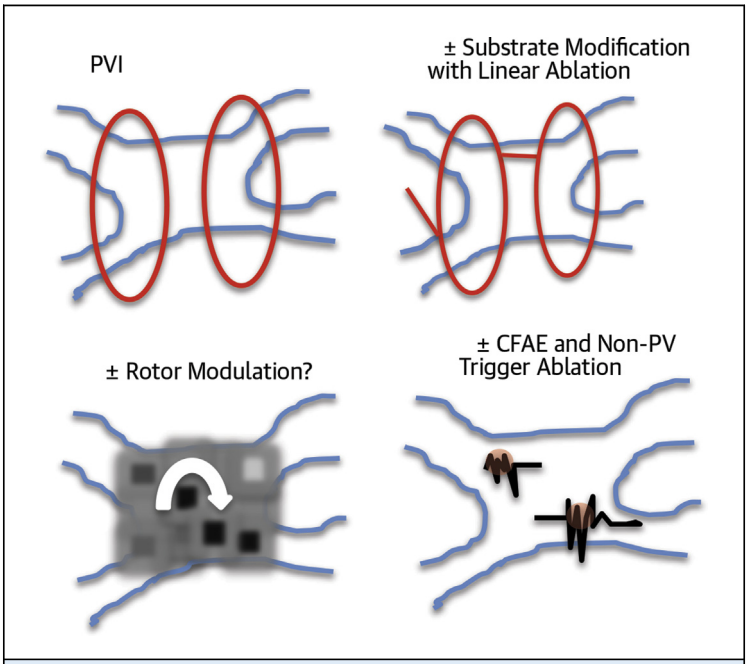


FIGURE 3 Approaches to Catheter Ablation in AF and HF

CFAE = complex fractionated atrial electrogram; PV = pulmonary vein; PVI = pulmonary vein isolation; other abbreviations as in Figure 1.

TABLE 1 Major Trials for Ablation of AF in Patients With HF

First Author (Trial Name) (Year) (Ref. #)	Study Type	N	Inclusion Criteria	AF Type	Intervention	Outcome Data
Chen et al. 2004 (65)	Cohort study	94*	Symptomatic AF, failed AAD with or without LV dysfunction	All types	PVI in reduced vs. normal EF	73% AF-free survival at 14 months; 96% AF-free off AAD after second procedure in those with reduced EF
Gentlesk et al. 2007 (66)	Cohort study	67*	Symptomatic AF, failed AAD with or without LV dysfunction	Paroxysmal and persistent	PVI in reduced vs. normal EF	86% AF-free survival in reduced EF group at 20 months; 14% mean improvement in EF with AF control
Khan et al. (PABA-CHF) 2008 (68)	Randomized trial	81	Symptomatic AF, NYHA class II–III HF, failed AAD, LVEF <40%	All types	PVI ± linear ablation of CFAEs vs. AV node ablation with BiV pacing	88% AF-free survival and significant increase in EF, functional capacity, and QOL in PVI group
MacDonald et al. 2011 (69)	Randomized trial	41	Persistent AF, NYHA class II–IV, LVEF <35%	Persistent AF	PVI ± linear and focal CFAE ablation vs. pharmacological rate control	50% AF-free survival in the PVI group at 6 months; nonsignificant increases in LVEF, functional capacity, and QOL; SR had significant increase in LVEF
Jones et al. (ARC-HF) 2013 (71)	Randomized trial	52	Persistent AF, NYHA class II–IV, LVEF <35%	Persistent AF	PVI ± linear and focal CFAE ablation vs. pharmacological rate control	88% AF-free survival in the PVI group at 12 months; significant increase in peak Vo_2, QOL, and pro-BNP compared with rate control arm
Hunter et al. (CAMTAF) 2014 (70)	Randomized trial	50	Persistent AF, NYHA class II–IV, LVEF <50%	Persistent AF	PVI ± linear and focal CFAE ablation vs. pharmacological rate control	81% AF-free survival in the PVI group at 6 months; significant increase in LVEF, improved LV ESV, functional capacity, BNP, and QOL

*Number of patients in reduced EF subgroup.

AAD = antiarrhythmic drug; AF = atrial fibrillation; AV = atrioventricular; BNP = B-type natriuretic peptide; BiV = biventricular; CFAE = complex fractionated atrial electrogram; EF = ejection fraction; ESV = end-systolic volume; HF = heart failure; LV = left ventricular; NYHA = New York Heart Association functional; PVI = pulmonary vein isolation; QOL = quality of life; SR = sinus rhythm; Vo_2 = oxygen consumption.

function measures (E′/E and LV strain) (72). Additionally, there were no major complications in the ensuing 36-month follow-up period.

Thus, the available data suggest that catheter ablation leads to maintenance of sinus rhythm in a substantial portion of patients with AF and HF. Furthermore, and perhaps more importantly, those undergoing PVI appear to have improved QOL and better neurohormonal profiles. As a result, guideline recommendations suggest that catheter ablation may be reasonable to treat symptomatic paroxysmal AF in patients with mild LV dysfunction (Class I, Level of Evidence: A) or significant LV dysfunction (Class IIb, Level of Evidence: A) (43). However, there is a need for larger randomized trials to adequately assess the safety and efficacy of ablation for achieving sustained sinus rhythm and improving functional capacity. Similarly, larger, multicenter trials will help explore the generalizability of results obtained from smaller studies. The much-anticipated RAFT AF (A Randomized Ablation-based Atrial Fibrillation Rhythm Control Versus Rate Control Trial in Patients With Heart Failure and High Burden Atrial Fibrillation) and CASTLE-AF (Catheter Ablation Versus Standard Conventional Treatment in Patients With Left Ventricular Dysfunction and Atrial Fibrillation) studies should help provide answers to these questions, with earliest results anticipated in 2016.

PROCEDURAL SAFETY. Although catheter ablation in patients with AF and HF has led to promising success rates in early studies, there remains room for improvement. Additionally, as with any percutaneous intervention, we see small but significant procedural risks. One meta-analysis of studies of catheter ablation in patients with LV systolic dysfunction estimated a 4.8% overall major adverse event rate, which included death, stroke, pulmonary vein stenosis, pericardial tamponade, and significant bleeding; there were no significant differences in adverse events between patients with or without reduced EF (73). The procedural risks also need to be considered in light of the fact that more patients with HF will require a repeat procedure compared with those without HF. It also stands to reason that procedural complication rates may be higher at institutions with lower procedural volumes.

EMERGING TECHNOLOGIES AND FUTURE DIRECTIONS

Ongoing clinical trials will help answer several important questions surrounding the safety and efficacy of catheter ablation of AF in patients with HF. In the meantime, numerous important questions

merit continued investigation (**Table 2**). Chief among these questions is whether or not the promising results achieved in smaller clinical trials will be observed in larger clinical studies. These larger studies will help provide needed data on the generalizability and effectiveness of catheter ablation. Long-term outcome studies are needed to help understand whether the benefits observed at 1 year after ablation are maintained in longer follow-up. This is a particularly important concern given the high risk for clinical progression and repeat hospitalization in patients with symptomatic HF. The impact of catheter ablation on HF hospitalization may have significant implications for its cost effectiveness, because hospitalizations for HF represent a major healthcare expenditure in many healthcare systems across the globe (12).

Beyond outcomes, important unanswered questions remain regarding the optimal technique for catheter ablation in patients with both paroxysmal and persistent AF. In particular, AF that is persistent and associated with HF has no standard acute procedural endpoints beyond PVI. Neither the optimal lesion set nor the appropriate endpoint of ablation has been determined. Some investigators advocate that termination of AF during ablation is an important endpoint because of an apparent association with freedom from AF (74–76). However, not all studies support termination of AF during ablation as an important endpoint (77), leading other investigators to prefer empiric lesion sets (78). The more longstanding an episode of AF, particularly when associated with structural heart disease or HF, the more complex the decision making. A limitation of current ablation procedures (and associated lesion sets) is the poor durability of endocardial lesions and conduction block. Emerging ablation technologies such as annotation algorithms based upon catheter stability and impedance drops (79), next-generation cryoballoon catheters (80), and contact-force sensing (81) offer the promise of more robust and durable lesion sets.

Should adjunctive ablation be performed in all patients with HF, only those with reduced EF, or only those with persistent AF (regardless of HF status)? The risk of recurrence is higher in patients with HF, yet the risk of proarrhythmia is likely to be increased as well. Finally, the role of newer mechanistic approaches, including FIRM and renal vein denervation, requires study. FIRM-guided ablation leads to improved freedom for AF when compared with PVI alone (82.4% vs. 44.9%; $p < 0.0001$) (57). These techniques have shown great promise in general AF ablation populations, but outside of promising small substudies in HF patients (82), their benefits to the wider AF population remain to be determined.

It is important to emphasize that the development of new technologies and techniques and their application to rhythm control in AF and HF require further and iterative evaluation, including any means of identifying critical substrate. For example, if the durability of PVI improves, many of the previous studies that look at adjunctive therapy may no longer be valid, and these strategies may need to be re-evaluated.

HYBRID AND SURGICAL ABLATION APPROACHES

Beyond pharmacological and catheter ablation approaches, there exist other methods of rhythm control in order to attenuate AF. The hybrid endocardial-epicardial ablation, or “convergent” procedure, was designed to be less invasive and avoid the need for chest incisions, lung deflation, and heart dissection (83). A transdiaphragmatic endoscopic approach is utilized to make gapped epicardial lesions, which are later connected via percutaneous mapping and endocardial ablation. Two prospective nonrandomized studies have demonstrated the general safety and efficacy of this procedure for treatment of drug-refractory AF (83,84), but only 16% of patients in these studies had comorbid HF, and the average LVEF was 55% to 58%. Gehi et al. (85) found similar results in a cohort of 101 patients, 30% of which had comorbid HF with an average pre-procedural EF of 50%.

TABLE 2 Key Questions Specific to Catheter Ablation of AF in Patients With HF

1. Does catheter ablation improve mortality compared with a pharmacological rate control strategy?
2. Is the efficacy of catheter ablation for AF dependent on the etiology of HF (ischemic vs. nonischemic)?
3. Are post-ablative improvements in functional capacity and quality of life preserved beyond 1 year?
4. Does catheter ablation reduce HF hospitalization at 1-year and longer follow-up?
5. Is catheter ablation cost effective in patients with HF?
6. Does catheter ablation improve freedom from antiarrhythmic drugs in long-term follow-up?
7. Is catheter ablation a viable first-line treatment of AF in patients with HF?
8. Does focal impulse rotor modulation improve maintenance of sinus rhythm over and above pulmonary vein isolation?
9. Should linear ablation be performed during a first catheter ablation procedure in all patients with HF (preserved and reduced EF)?
10. Should termination of AF be a goal of ablation in patients with HF and persistent forms of AF?
11. Does catheter ablation improve long-term renal function in patients with HF?
12. Does renal denervation improve maintenance of sinus rhythm in hypertensive HF patients undergoing catheter ablation?

Abbreviations as in **Table 1**.

Arrhythmia-free survival was 66% at 12 months after a single procedure and 71% after repeat ablation with a major periprocedural complication rate of 6%.

The Cox-Maze III procedure is the surgical standard for medical-refractory AF. It is most often performed in the setting of concomitant valve surgery and/or revascularization procedures, and is associated with decreased AF burden without significant complications when compared with usual surgical care (86). The traditional cut-and-sew approach serves as the gold standard for conduction block because it provides definitive transmural injury to cardiac tissue, whereas catheter ablation and hybrid approaches create endocardial and endocardial/epicardial lesions, respectively. Overall, the strength of evidence for surgical maze procedures versus usual surgical care, in regard to restoration and maintenance of sinus rhythm, is reasonable yet insufficient when considering post-procedural HF symptoms and QOL (87). There is limited evidence when comparing the cut-and-sew approach to other surgical maze modalities (radiofrequency, microwave, or cryothermy), though retrospective data are suggestive of cut and sew being superior in achieving freedom from AF (88,89). Few data are available describing outcomes in patients with LV dysfunction and/or HF who undergo surgical ablation. In a series of 42 patients with AF, a LVEF <40% and symptomatic HF undergoing cardiac surgery with concomitant Cox-Maze III/IV procedures, 86% of patients were in sinus rhythm at a median of 6 months (90). The average improvement in LVEF was 15%, and perioperative mortality was 2%. These data suggest that surgical ablation in patients with HF and significant LV dysfunction may be possible without significant added operative risk. Similar to other rhythm control interventions in the AF/HF population, additional studies are warranted.

CONCLUSIONS

In this ever-expanding population of patients with concomitant AF and HF, it is apparent that sinus rhythm provides improved ventricular function, physical function, and overall QOL. Catheter ablation offers a superior approach to achieving sinus rhythm compared with antiarrhythmic drug therapy alone, especially when considering the few available agents for use in patients with HF. Although there are limited studies reporting on major cardiovascular outcomes following catheter ablation in patients with HF, recent trials note improvement in prognostic surrogates for HF outcomes as well as QOL. Future studies, including large randomized trials, will help delineate the utility of this procedure in reducing morbidity and, perhaps, mortality in patients with concomitant AF and HF.

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